

## REMARKS

Upon entry of the present amendment, claims 1-20 are pending. In the present Amendment, Applicants have amended claims 1 and 2 to recite "and having a sedimentation velocity of 0.8 cm/s or lower." Support for that amendment is provided in the specification, for example, at page 20, lines 5-8. Applicants have also added new claims 18-20. Claims 18-20 are supported by claim 1 as originally presented in the Preliminary Amendment filed March 15, 2004, and as indicated below. Claim 18 is supported in the specification, for example, at page 9, lines 10-15. Claim 19 is supported, for example, by claim 3. Claim 3 recites zinc-containing  $\beta$ -tricalcium phosphate and  $\text{CaZn}_2(\text{PO}_4)_2$  (i.e.,  $\text{CaZn}_2(\text{PO}_4)_2 \cdot n\text{H}_2\text{O}$  ( $0 \leq n \leq 2$ ), where  $n=0$ ). This positive recitation of zinc-containing  $\beta$ -tricalcium phosphate and  $\text{CaZn}_2(\text{PO}_4)_2$  supports the exclusion of those compounds from claim 19. See MPEP § 2173.05(i) at 2100-215 (8<sup>th</sup> ed. rev. 2, May 2004) (citing *In re Johnson*, 558 F.2d 1008, 1019, 194 USPQ 187, 196 (CCPA. 1977)). Claim 20 is supported, for example, by claim 3. No new matter is added by the foregoing amendments.

### I. Rejection of Claims 1-17 Under 35 U.S.C. § 103(a)

The Examiner rejected claims 1-17 under 35 U.S.C. § 103(a) as allegedly being unpatentable over Otsuka *et al.*, J. Biomed. Mater. Res. (2000) 52:819-824 ("Otsuka 2000") or Otsuka *et al.*, *Bioceramics*, Vol. 12, from Proceedings of the 12<sup>th</sup> International Symposium on Ceramics in Medicine, Nara, Japan, October 1999, eds. H. Ohgushi *et al.*, pp. 571-574 ("Otsuka 1999"), each in further view of EP 0 702 954.

Specifically, the Examiner alleged that Otsuka 1999 and Otsuka 2000 "disclose an amount of 0.6% of zinc. Zinc in the amount of 0.6% is close enough to 0.568% [the

upper limit of the claimed range of zinc concentration] such that one of ordinary skill in the art would expect that the zinc calcium phosphate compounds would exhibit the same properties.” Office Action at page 3.

Without acquiescing to that rejection and solely to expedite prosecution of the present application, Applicants have amended claims 1 and 2 to recite “having a sedimentation velocity of 0.8 cm/s or lower.” Neither Otsuka 2000 nor Otsuka 1999 even mention sedimentation velocity, let alone the specific sedimentation velocity of 0.8 cm/s or lower recited in claims 1 and 2. Thus, the cited documents would have failed to teach or suggest all the elements of claims 1 and 2. For that reason alone, the Examiner has failed to establish a *prima facie* case of obviousness.

Moreover, the Federal Circuit has warned against using “a retrospective view of inherency” as a substitute for some teaching or suggestion supporting an obviousness rejection. See *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993). “The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic. MPEP § 2112 at 2100-54 (8<sup>th</sup> ed. rev. 2, May 2004) (citing *In re Rijckaert*, 28 USPQ2d at 1957). Neither of the Otsuka references discuss sedimentation velocity, let alone a sedimentation velocity of 0.8 cm/s or lower. Sedimentation velocity depends on a number of variables, including the viscosity of the solvent, the specific gravity of the solvent, the size of the particle, and the specific gravity of the particle (which depends, in turn, on factors such as the air content of a porous particle). See, e.g., specification at page 19, line 11, through page 20, line 5. Otsuka 1999 provides no information on the size or specific gravity of the disclosed particles. Otsuka 2000 discusses size (see page 820, col. 1), but not specific

gravity, of the disclosed particles. Thus, there is no indication that the particles of Otsuka 1999 and Otsuka 2000 have a sedimentation velocity of 0.8 cm/s or lower.

Applicants also point out that obviousness cannot be predicated on a property of a prior art composition that is unknown but which may be inherent. See *In re Rijckaert*, 28 USPQ2d 1955, 1957 (Fed. Cir. 1993) (cited in the MPEP § 2112 at 2100-154 (8<sup>th</sup> ed. rev. 2, May 2004) (“That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown.”). The sedimentation velocity of the particles discussed in Otsuka 1999 and Otsuka 2000 is neither taught nor suggested. Thus, the Otsuka references cannot provide the basis for obviousness of the claims 1 and 2, which recite a specific sedimentation velocity of 0.8 cm/s or lower

And, although the Examiner did state that he considered the invention “as a whole” in assessing obviousness, it appears that the Examiner was more focused on the individual elements. As is well established, “[i]n delineating the invention as a whole, we look not only to the subject matter which is literally recited in the claim in question ... but also to those properties of the subject matter which are inherent in the subject matter *and* are disclosed in the specification.” See *In re Antonie*, 195 USPQ 6, 8 (C.C.P.A. 1977) (cited in MPEP § 2144.05 II.B. at 2100-143). “The controlling question is simply whether the differences...between the prior art and [the] invention as a whole are such that [the] invention as a whole would have been obvious.” *Id.*

In *In re Antonie*, the appellant claimed a wastewater treatment device having a ratio of “tank volume to contractor area” of 0.12 gal./sq. ft. *Id.* at 7. In considering the invention as a whole, the court determined that the recited ratio maximized the “treatment capacity” of the device. *Id.* at 8. Although the prior art taught “the basic structure of the device claimed by appellant,” it was silent regarding the ratio of tank

volume to contractor area. *Id.* at 7. In fact, the prior art failed to appreciate the factors that contribute to that ratio, precisely because the prior art “was not trying to maximize or control ‘treatment capacity’.” *Id.* at 8. Accordingly, the court found that the prior art failed to recognize that the ratio of tank volume to contractor area affected the “treatment capacity” of the device. *Id.* Thus, the court concluded that the claimed device was not obvious over the prior art, because “the parameter optimized [i.e., the ratio] was not recognized to be a result-effective variable.” *Id.* at 9.

The same reasoning applies to the instant claims. According to the Applicants’ disclosure, “[w]hen administered to an animal or human, it is required that the microparticles should be dispersed without sedimentation. Therefore, sparingly soluble zinc-containing calcium phosphate should be kept dispersed in the solvent for a predetermined period of time when administered....” Specification at page 18, lines 2-6. Claims 1 and 2 recite a sedimentation velocity of 0.8 cm/s or lower. That sedimentation velocity allows the microparticle to “be kept suspended in the solvent” for a suitable amount of time to allow administration of the suspension to an animal or human. See specification, e.g., at page 18, lines 8-20. Thus, the recited sedimentation velocity allows for effective administration of the claimed suspension to an animal or human.

Neither Otsuka 1999 nor Otsuka 2000 recognized that the sedimentation velocity of a microparticle of zinc-containing calcium phosphate is a “result-effective variable” in the administration of a microparticle to an animal or human. Moreover, none of the experiments discussed in Otsuka 1999 or Otsuka 2000 considered the effects of the specific gravity of the particle, the size of the particle, the specific gravity of the solvent, and the viscosity of the solvent on sedimentation velocity, because those references did not seek to optimize sedimentation velocity.

Indeed, it is the Applicants' own extensive experimentation that shows how different zinc-containing calcium phosphate microparticles have different sedimentation velocities depending on their zinc content, particle size, and solvent. *See, e.g.*, pages 24-31, Examples 1-5. By experimentally measuring the sedimentation velocities of various particle/solvent combinations, the Applicants identified exemplary suspensions comprising particles having the claimed sedimentation velocity of 0.8 cm/s or lower. *Id.* Thus, Applicants recognized sedimentation velocity as a result-effective variable and provided extensive disclosure relating to optimization of that parameter using different particle/solvent combinations.

The Otsuka references, however, did not even consider sedimentation velocity. Thus, the Otsuka references failed to recognize sedimentation velocity as a "result-effective variable" in the administration of a zinc-containing calcium phosphate microparticle to an animal or human. Thus, the Otsuka references would have failed to render obvious the invention of claim 1 or 2 "as a whole."

For at least the above reasons, Otsuka 1999 or Otsuka 2000 would not have taught or suggested the invention of claims 1 or 2 "as a whole." EP 0 702 954 would have failed to cure this deficiency. EP 0 702 954 discloses a dietary supplement that may include, for example, emulsifiers, solvents, or suspending agents. *See, e.g.*, page 3, lines 9-12 and 18-20. Applicants point out that EP 0 702 954 does not disclose any of the specific water-immiscible solvents recited in claims 6 and 12-13. Regardless, EP 0 702 954, like the Otsuka references, fails to mention sedimentation velocity, let alone to suggest any importance associated with sedimentation velocity, or to direct one skilled in the art to determine sedimentation velocity. Thus, the cited documents, either

singly or in combination, would have failed to teach or suggest the invention of claims 1 or 2 “as a whole.”

## **II. New Claims 18-19 Are Patentable**

### **New Claim 18**

New claim 18 recites “wherein said microparticle comprises zinc-containing calcium phosphate *glass*” (emphasis added). Neither Otsuka 1999 nor Otsuka 2000 discuss zinc-containing calcium phosphate glass. Furthermore, the specification teaches that zinc-containing calcium phosphate glass is obtained by heating soluble zinc-containing calcium phosphate to a temperature of “980°C or higher.” Specification at page 9, lines 10-15; see *also* Example 1 at page 24, lines 16-19 (discussing heating to 1000°C). Otsuka 2000 discusses heating a precipitate to only 850°C. Otsuka 1999 does not discuss temperature. Thus, the Otsuka references would not have taught or suggested a microparticle containing zinc-containing calcium phosphate glass. Because the Otsuka references would have failed to teach that element, the Otsuka references would have failed to render obvious the composition of new claim 18.

Furthermore, one skilled in the art would not expect a microparticle comprising zinc-containing calcium phosphate glass to exhibit the same properties as the particles disclosed in the Otsuka references. One skilled in the art would readily recognize that a microparticle comprising zinc-containing calcium phosphate glass would be structurally distinct and thus would have different properties, for example, with respect to solubility and the timing of zinc release from the microparticle. Thus, the Otsuka references would have failed to render obvious the composition of new claim 18.

**New Claims 19 and 20**

New claims 19 and 20 both recite “having a sedimentation velocity of 0.8 cm/s or lower.” Thus, Otsuka 1999 and Otsuka 2000 would not have taught or suggested the invention of new claims 19 and 20 for the reasons discussed above, Part I.

Further, Otsuka 1999 and Otsuka 2000 would not have taught or suggested all the elements of new claims 19 and 20. New claim 19 recites “wherein the zinc-containing calcium phosphate does not comprise zinc-containing  $\beta$ -tricalcium phosphate or  $\text{CaZn}_2(\text{PO}_4)_2$ .” Otsuka 2000 discusses powders of zinc containing tricalcium phosphate (“ZnTCP”). The ZnTCP powders of Otsuka 2000 are powders of zinc-containing  $\beta$ -tricalcium phosphate and, in some cases,  $\beta$ - $\text{CaZn}_2(\text{PO}_4)_2$ . See page 820, col. 2 and page 821, col.1. Thus, new claim 19 excludes the ZnTCP powders of Otsuka 2000.

Like Otsuka 2000, Otsuka 1999 also discusses ZnTCP powders. Although Otsuka 1999 uses the general term “ZnTCP” without expressly stating that the ZnTCP is zinc-containing  $\beta$ -tricalcium phosphate, one skilled in the art would understand that this is indeed the case. Otsuka 1999 appears in the Proceedings of the 12<sup>th</sup> International Symposium on Ceramics in Medicine, Nara, Japan, October, 1999. The Otsuka 1999 article is immediately preceded in the Proceedings by an article by Ito *et al.* See Ito *et al.*, *Bioceramics*, Vol. 12, from Proceedings of the 12<sup>th</sup> International Symposium on Ceramics in Medicine, Nara, Japan, October 1999, eds. H. Ohgushi et al., pp. 567-570 (“Ito 1999”), cited in the Information Disclosure Statement filed herewith. Like Otsuka 1999, Ito 1999 also discusses ZnTCP and is co-authored by some of the co-authors of Otsuka 1999 (A. Ito, P. Layrolle, and N. Ichinose). Both Ito 1999 and Otsuka 1999 are

individual reports within a series on ZnTCP. Ito 1999 discusses ZnTCP in ceramics.

Otsuka 1999 discusses ZnTCP powders in liquids.

The Abstract of Ito 1999 states that “Zinc was doped into  $\beta$ -tricalcium phosphate up to 10 mol %. The zinc-doped tricalcium phosphate (ZnTCP)....” Ito 1999, page 567.

Ito 1999 further states that “...zinc-containing  $\beta$ -TCP (ZnTCP:  $\text{Ca}_{3-x}\text{Zn}_x(\text{PO}_4)_2$ ) could function as a zinc-releasing biomaterial....” Ito 1999, page 568, first full paragraph.

Thus, one skilled in the art would understand that the ZnTCP of Ito 1999 is zinc-containing  $\beta$ -tricalcium phosphate. Likewise, one skilled in the art would understand that the ZnTCP of Otsuka 1999 is also zinc-containing  $\beta$ -tricalcium phosphate, based on the fact that Otsuka 1999 appears in the same Proceedings as Ito 1999 and shares some of the same authors as Ito 1999. Accordingly, new claim 19 excludes the ZnTCP powders of Otsuka 1999.

New claim 20 recites “wherein said microparticle of zinc-containing calcium phosphate comprises one or more compounds selected from zinc-containing calcium hydrogenphosphate, zinc-containing amorphous calcium phosphate, zinc-containing  $\alpha$ -tricalcium phosphate, zinc-containing poorly-crystallized apatite,  $\text{CaZn}_2(\text{PO}_4)_2 \cdot \text{H}_2\text{O}$ , and  $\text{CaZn}_2(\text{PO}_4)_2 \cdot 2\text{H}_2\text{O}$ .” Neither Otsuka 1999 nor Otsuka 2000 teaches any of those compounds.

Moreover, neither Otsuka 1999 nor Otsuka 2000 would have suggested the compounds recited in claim 20. Otsuka 2000 teaches producing ZnTCP powders by calcining a precipitate at 850°C for 3 hours. See page 820, Materials. Otsuka 1999 is silent as to how ZnTCP is produced. The conditions of Otsuka 2000 for producing ZnTCP are different from the exemplary conditions Applicants disclose for producing the

compounds recited in claim 20. For example, the specification discloses different reaction temperatures than the 850°C reaction temperature of Otsuka 2000:

<u>Zinc-containing Calcium Phosphates</u>	<u>Reaction Temperature</u>
zinc-containing calcium hydrogen phosphate	room temp. (Example 5, p. 30) no heating (p. 9, lines 25-29)
zinc-containing amorphous calcium phosphate	no heating (p. 9, lines 25-29)
zinc-containing $\alpha$ -tricalcium phosphate	1400°C (Example 4, p. 29) 1150-1500°C (p. 10, lines 26-28)
zinc-containing poorly-crystallized apatite	no heating (p. 9, lines 25-29)
$\text{CaZn}_2(\text{PO}_4)_2 \cdot \text{H}_2\text{O}$	no heating (p. 9, lines 25-29)
$\text{CaZn}_2(\text{PO}_4)_2 \cdot 2\text{H}_2\text{O}$	room temp. (Example 5, p. 30) no heating (p. 9, lines 25-29)

Thus, the teachings of Otsuka 2000 would not have suggested arriving at the compounds of claim 20.

### III. Summary

The Examiner has failed to establish that claims 1 and 2 would have been obvious. Claims 3-17 ultimately depend from claims 1 or 2. Thus, those claims would not have been obvious. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 1-17 under 35 U.S.C. § 103(a). Applicants also assert that new claims 18-20 would not have been obvious over the cited documents.

### CONCLUSION


Applicants respectfully assert that the application is in condition for allowance. If the Examiner does not consider the application to be in condition for allowance, Applicants request that the Examiner call the undersigned at (650) 849-6778 to arrange an interview prior to taking action.

Please grant any extensions of time required to enter this response and charge  
any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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